Histogenesis of Hypernephroma

by

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HISTOGENESIS OF HYPERNEPHROMA

Classification of parenchymatous renal tumors has been a source of much dispute among pathologists largely due to disagreement concerning the genesis of a group often termed hypernephroma and lack of unity of opinion as to what tumors should be placed under this heading.

The name "hypernephroma" originated in the belief that they were of adrenal cortex origin. Some authors have included in this class nearly all renal tumors other than the embryonal sarcoma of infants, the rare sarcoma of adults and the occasionally reported fibroma, lipoma or myoma. Many have considered only a limited number of these to be of adrenal rest origin but cling to the term "hypernephroma" because of popular usage. Others place a large number of kidney tumors under the headings of renal adenoma and carcinoma and designate a varying number ad renal hypernephroma.

It is obviously difficult, in discussing renal tumors to use a term or terms applying to them, which will

make the scope considered, comprehensive. This makes it necessary then to define those discussed, not by name, but by description.

By the term "hypernephroma" I would designate a group of tumors described as occurring in the parenchyma of the kidney and presenting a microscopic picture suggesting adrenal cortex. Such a description does not clearly separate these tumors from other renal tumors of the frank carcinoma or adenoma type. The latter are recognized to be of renal tissue origin and yet no distinguishing feature separates them from the hypernephroma in many instances. Certain features are common to all and some of one class merge insensibly with those of another.

This has been responsible for much of the confusion arising in regard to their genesis. Considerable argument has been contributed pointing to an adrenal origin of some of the tumors, and a renal origin for others and yet separation into distinct groups according to genesis has not been satisfactorily accomplished.

Nearly all authors admit the renal origin of some

of the tumors defined here under hypernephromas. If this is true, then the term is plainly a misnomer in these cases. But because of the general application of the term to this class of kidney tumors, it seems best to designate them as such in this discussion in which an attempt will be made to point out the various subgroups according to genesis and characteristics displayed.

Purpose of Thesis

I have undertaken here to show that these so-called hypernephromas, while having many characteristics in common, possess features, in the majority of cases, which make it possible to establish their origin, and that this origin may possibly be in some cases (1) adrenal cortex rests in the kidney but in the vast majority of cases is undoubtedly (2) renal epithelium. And further that it is sometimes possible to separate the latter class into (a) those originating from adult renal epithelium and (b) those from embryonal renal epithelial rests sometimes found in the kidney.

Incidentally in describing the development of the renal tumors from their parent tissues it will be shown

that the benign adenoma passes insensibly into the malignant tumors, and while a class of tumors may justly be referred to as renal alveolar-adeno-carcinomas no clear-cut line of distinction exists between them and malignant renal adenomas.

History.

Early observations of renal tumors led to a desription of the hypernephroma group under a variety of names, eg: "angiosarcoma, endothelioma, lipoma, carcinoma and alveolar sarcoma". In 1883 Grawitz published a paper expressing the opinion that the greater number of these tumors belonged to a single type and that they originated in the kidney from misplaced bodies of adrenal cortex tissue. Their similarity of histologic appearance to primary adrenal cortex tumors, their location beneath the kidney capsule, perfect encapsulation, and the frequent presence of a fibrous tissue core were the chief reasons for this conclusion.

Grawitz called these tumors "strumae lipomatodes

aberratae renis". Birch-Hirshfeld suggested the simpler term "hypernephroma".

This theory possessed many reasonable features. Both primary adrenal cortex tumors and many kidney tumors were made up of cells with a high lipoid content, the individual cells peculiarly lacking in degeneration. It was accepted also that adrenal cortex tissue was often seen beneath the kidney capsule where hypernephroma seemed to develop. Primary adrenal cortex tumors often were characterized by a distinct core of fibrous tissue not unlike that often seen in hypernephromas of the kidney and this strengthened the general similarity of appearance of the tumors.

A large number of papers followed that of Grawitz both agreeing with and disputing his theory. Lubarsch added considerable weight to Grawitz's argument by emphasizing the glycogen content of hypernephromas and adrenal tumors and its relative absence in other tumors. It was later shown to be present in most neoplasms, however, and this phase of the argument lost its importance.

Horn, Kelly and Beneke soon followed with papers

agreeing with Grawitz.

In 1893 Sudeck published results of his study tracing hypernephromas to adult renal tubules or small adenomas developing from them. It was not until 1908 that Sudeck's work was given deserved attention. Stoerk at this time contended Sudeck's opinion was correct. His work was based on the study of one hundred and twenty renal tumors. He pointed out the relative frequency of occurrence of hypernephromas in the kidney and their rarity in the adrenal. He also noted the general distribution of the kidney tumors and the relatively high incidence of adrenal rests in the upper pole.

Chemical analysis, in an attempt to find evidence of adrenalin in hypernephromas, was made by a number of writers (Greer and Wells, Federoff, Crofton). Results were inconclusive but this is of little importance for it has been well demonstrated that it is the adrenal medulla and not the cortex in which adrenalin is found.

Wilson and Willis in 1910 studied the embryological

development of the adrenal and kidney and concluded that at a time when the anlage of these organs were closely associated, a band of fibrous tissue separated them, thus making impossible the misplacement of adrenal tissue in the kidney. They advanced the hypothesis that hypernephromas originated in Wolffian body rests. In 1926 Bothe refuted the Wilson and Willis work in a similar study by demonstrating in many cases a deficiency in the fibrous tissue separating kidney and adrenal anlage. He found nothing precluding the possibility of adrenal rests occurring in the kidney.

Some earlier writers traced hypernephromas to perithelial cells (DePaoli) and endothelial cells of blood and lymph vessels (Driessen) but scant attention has been given to these views in late years.

The greater part of the argument concerning genesis has been centered about the idea of adrenal rest origin of renal tumors. Most recent writers agree that some hypernephromas arise from kidney epithelium but as to the relative number a wide variation of opinion exists (Ewing,Karsner).

ADRENAL REST ORIGIN OF HYPERNEPHROMA

Hypernephromas in general have a striking microscopic and gross appearance strongly suggesting adrenal tissue.

However, the kidney and adrenal cortex are both of early mesenchymal origin. The anaplastic tendency of tumors is well recognized and in such a case tumors of adrenal cortex and renal epithelium might well be expected to have considerable in common.

Moreover, the epithelium of renal parenchyma and adrenal cortex, originating in mesenchyme, is not epithelium in the strict sense. This places tumors developing from either in a unique class and calls for careful observation to determine the presence of characteristics that may separate them.

If it were possible to trace renal tumors to adrenal cortex tissue or to renal epithelium directly their genesis would be obvious. However, this is difficult in most cases, the original tissue being overgrown by the tumor. In the case of adrenal tissue few men have succeeded in conclusively accomplishing it.

It is then necessary to rely on characteristics of primary adrenal cortex tumors, differing from those of primary renal tumors, to identify adrenal tumors occurring in the kidney.

Misplacement of Adrenal Cortex Tissue in the Kidney.- Study of the embryological development of the adrenal has demonstrated the liklihood of small areas of foetal adrenal cortex tissue becoming separated from their anlage. These small bodies of tissue are frequently seen in the embryos attached to the adrenal by a slim pedicle or completely separated from it, lying free in the surrounding loose connective tissue (Elliot and Armour).

The adrenal cortex develops from the urogenital ridge as does the kidney. In the earlier stage the metonephrogenic tissue is located at considerable distance from the adrenal body which is considerably larger at that period (Keibel and Mall). Wilson and Willis pointed out that at the time these two structures come into closer relation they are separated by a well formed band of connective tissue. This was the basis for their argument of the impossibility of adrenal

cortex rests finding their way beneath the kidney capsule.

Bothe, however, working along the same line found that in many cases, at a time when adrenal and renal anlage came close together, the separating band of connective tissue was deficient and no barrier existed to the possible misplacement of small bodies of adrenal tissue in the kidney.

The finding of pinhead to pea size nodules of adrenal cortex tissue beneath the kidney capsule and even in the kidney parenchyma has been prepeatedly reported. Frequency of this occurrence has been variously estimated. Dunn found three such rests in the kidneys from eighty consecutive autopsies. Kettle, Glynn and others have found a much lower incidence. They have been frequently reported as occurring in the liver, spermatic cord, ovaries, testes, uterus and broad ligament, and that they are not found more often in these locations Kettle believes due to lack of diligence in searching for them.

In a specimen I examined a nodule 8 mm. in diameter was found in the kidney capsule causing a depression in the cortex. Histological examination shows

it to be, without doubt, an adrenal cortex tissue misplacement.

The finding of the entire adrenal beneath the kidney capsule has been described by Grawitz, Dunn, Hall and others. I have also examined a case in which both adrenals were situated beneath the kidney capsule and slightly embedded in the kidney parenchyma. A number of small arteries penetrating the kidney cortex furnished the adrenal blood supply.

Distribution in the Kidney of Adrenal Rests and Hypernephromas.- The distribution of adrenal rests in the kidney is almost limited to the upper pole. In studying statistics on the location of hypernephroma in the kidney we find that they are as frequent in the lower pole and middle portion of the kidney as in the upper pole (Küster).

Among the combined group of cases studied at the Halstead Hospital and at the University of Kansas Medical School, which were diagnosed hypernephroma because of their marked histological similarity to adrenal cortex, 8 were found at the upper pole, 9 at the lower pole and 3 arose from the mid-portion of the kidney.

This alone should cause serious doubt that all hypernephromata of the kidney arise in adrenal cortex rests. It does not preclude, however, the possibility that some hypernephroma do have their origin in these rests.

If it is true that kidney tumors do arise in rests of normal-appearing adrenal cortex they would be expected to possess much the same characteristic as primary tumors of the cortex of the adrenal.

Primary Adrenal Cortex Tumors.- Primary tumors of the adrenal cortex are rare. Few collections of size have been assembled and material to which I have had access has been limited. For that reason it has been necessary to draw heavily on the literature for description and case histories of these tumors and this is used in comparing the cortical adrenal tumors and hypernephromas.

In a high percentage of adrenals examined at autopsy areas of hyperplasia of the cortex may be found (Lubarsch 33 per cent). These may be almost microscopic in size but sometimes become as large as an orange. Smaller tumors have been considered simple hyperplasia. It is difficult to say which are only examples of

hyperplasia and which neoplastic as some of the larger specimens are undoubtedly adenomata.

Ewing describes the progressive development of these adenoma with all the characteristics of a carcinoma and applies the term "adeno-carcinoma" to them.

Lubarsch casts considerable doubt on the existence of a malignant adrenal cortex tumor occurring, believing many of the reported cases to be of metastatic origin.

It is difficult to prove the malignant characteristics of adrenal tumors because of the small size of the adrenal and the fact that tumors arising from it would soon attach themselves to surrounding organs from which it might appear the tumor arose. Because of the uncertainty which now exists concerning even the actual existence of some malignant adrenal tumors it seems best to eliminate them from discussion here. Moreover it seems that the adenomatous type of adrenal tumor, whether malignant or benign, is the only one with which we are concerned here as it alone resembles the hypernephroma of the kidney.

The gross appearance of most adrenal cortex neoplasms

of this type is described as characterized by encapsulation, a lobular appearance and a moderately elastic consistency. There is some tendency to degeneration with frequent interstitial hemorrhage in malignant tumors. The predominant color of the cut surface is yellow or yellowish-gray showing a high lipoid content. In malignant tumors a fibrous core has been described. This sometimes constitutes as much as one-fourth the entire bulk of the tumor.

The histological appearance of these tumors varies greatly. The majority, however, are adenoma or carcinoma having an alveolar structure. Their cells are large, polyhedral or somewhat columnar, having relatively small nuclei staining deep with basic dye. The cytoplasm appears markedly vacuolated in the section prepared in alcohol. This is due to a high lipoid content of the cells which is dissolved in the process of sectioning. The result is a foam-like appearance of the cytoplasm.

The structure of adrenal tumors depends in some measure on the stratum of the cortex from which they arise. Sheets and columns are frequent and resemble

the zona faciculata. An alveolar structure is common in both adenoma and carcinoma.

The stroma consists almost entirely of fine anastomosing capillaries whose walls are a single layer of endothelium. Only occasionally are fibrous strands seen surrounding these capillaries. The cells are in intimate contact with the capillary walls.

There has been much discussion concerning the actual, or possible, presence of lumen in the alveoli of adrenal tumors. None have been demonstrated beyond dispute and many of those recorded as lumen may be accounted for by the degeneration of centrally located cells.

Lubarsch has pointed out the presence of lumen in the normal adrenal cortex of the horse. None ever appears in the normal human adrenal. There is then no reason to expect structures possessing lumen to appear in neoplasms of the adrenal and if such do occur they are always of doubtful character.

The same may be said of the presence of papilliferous structure in adrenal tumors. Without lumen in alveoli, or other cavities into which papillations

may project, their formation is not to be expected. Columns do form resembling the zona faciculata of the adrenal and these sometimes suggest papillations in sections but the presence of definite papillations cannot be demonstrated.

The physiological function of the normal adrenal cortex is not well understood but is known to be related to the development of secondary sexual characteristics. Many adrenal cortex tumors are associated with symptoms of abnormal sexual function. In a series of cases collected by Glynn various perversions of sexual function were noted and the syndrome described by him which has been used often in the diagnoses of these tumors preoperatively.

When these sexual changes occur in children they take the form of precocious development of genital organs, appearance of pubic hair, and maturing of the voice. Girls sometimes develop menstrual flow. When the tumors develop in women during the child-bearing period menstruation becomes scant and irregular or ceases. Hair develops on the face and chest, the breasts atrophy, the facies become masculine, the voice

deep and muscular development is noticeable. Glynn states there is probably little or no change in the male adults.

Comparison of Primary Adrenal Cortex Adenomatous Tumors and Hypernephromas of the Kidney.- The gross appearance of the renal tumors, considered here as hypernephromas, are in general quite similar to the adenomatous type of primary adrenal cortex tumors. They have the same tendency to be well encapsulated and have a somewhat lobulated external appearance. The cut surface usually shows evidence of hemorrhagic degeneration, this often being so extensive as to form cysts. The color is of the same yellowish gray as the adrenal tumors.

Two hypernephroma of the kidney which I have examined have a well defined fibrous core. Grawitz pointed this out as characteristic of primary adrenal tumors and considered their presence in kidney tumors proof that the tumor originated in adrenal rests. In my cases this does not appear true. Neither displayed any of the distinctive features of adrenal cortex tumors.

On the contrary they did possess the microscopic characteristics of a group of tumors that will be described later as hypernephromas of renal origin.

Microscopic comparison of these two classes of tumors reveals much in common. However, there are features which separate clearly, in a large number of cases, tumors arising from kidney epithelium and primary adrenal cortex tumors.

The greater part of the so-called renal hypernephromas are characterized by the presence of large, clear, polyhedral or elongated cells sometimes having the appearance of foam cells. The nucleus is moderately large and vacuolated, but stains deep with basic dyes. Even in the papillary tumors to be described later, whose stroma is largely covered with deep staining granular cells, we may nearly always find areas of clear, vesicular cells.

Primary adrenal cortex tumors, of adenomatous character, are largely composed of identical cells so far as it is possible to determine. This similar or identical appearance of cells has been the initial factor leading to the confusion that has arisen concerning genesis of

the hypernephromas.

The stroma of both types of tumors is sufficiently similar as to escape differentiation by any methods thus far used. In the hypernephromas it is largely made up of thin capillaries of a single layer of endothelium. In the predominating type no fibrous tissue separates these from the cells of the tumor. This is by no means always the case, however, as may be demonstrated by examining sections stained especially for identification of fibrous tissue. Trabeculations of fibrous tissue carrying larger vessels separate the tumors into lobulations similar to the arrangement of bosselated goiters.

In examining the structure we meet with characteristics which are not common to all tumors of these classes. Clear-cut papillations and acini with distinct lumen are present, without doubt, in by far the majority of hypernephromata of the kidney. It is true that in many areas in these tumors there is no intimation of this structure. Here alveoli, columns and sheets are seen. Wright has demonstrated by serial section the cause of such an appearance. Sections at various levels through papillation may result in slides showing

any of these arrangements of cells and stroma. I was able to demonstrate tubules, acini or papillations in all hypernephromata examined in which sufficient sections were made. Often papillations are covered with many layers of cells and the tangled papillations, the development of which is described later, sometimes make it difficult to analyse the structure until a section through the proper plane is made.

There are vesicular cell tumors reported occurring in the kidney, however, in which the structure was acinar and columnar and in which no lumina or papillations were found. They are by far in the minority compared to the type just described. Gross appearance does not allow differentiation. Some of these, perhaps, would reveal characteristics of the papillary and acinous type if more carefully examined but some undoubtedly would not. These may be of adrenal rest origin and some few cases reported probably are, as they seem to possess, in certain instances, physiological properties causing sexual abnormalities often seen in adrenal cortex tumors.

Reported Cases of Renal Tumors Accompanied by Abnormal Sexual Changes.

Several cases of kidney tumors and extra-adrenal hypernephroma in other locations, associated with abnormal sexual changes are found in the literature (Fraser, Jumps, Beates and Babcock, Merrion and Smith, and Feinblatt). Some of these are reported as adrenal tumors rather than renal hypernephroma but these are attached to the kidney, and were it not for the symptoms of sexual disturbance produced, would no doubt, have been considered renal tumors.

Feinblatt's case is an excellent example of this. Gross pictures of the tumors are typical of that usually portrayed as hypernephroma. The patient, a young woman, developed marked masculine characteristics. This led to a preoperative diagnosis of adrenal cortex tumor.

Fraser's case was quite similar to Feinblatt's but is considered by the writer a renal tumor of adrenal tissue origin.

In a series of eleven cases of primary hypernephroma of the ovary, collected by Downes and Knox, five of

the patients had abnormal sexual changes or menstrual disturbances.

The structure of these tumors is uniformly described by the writers as typical adrenal cortex tumors and as having no papillations or acini with distinct lumen.

Definition of Renal Hypernephromas of Adrenal Cortex Origin.- In separating from the hypernephromata group of kidney tumors those of adrenal rest origin we must first consider the structure. If it is not possible to demonstrate papillations, tubules or definite acini we are then permitted to consider the neoplasm as possibly arising from adrenal cortex tissue. Of these a few may, in the earlier stages, be directly traceable to adrenal rests or ectopic adrenals and the diagnosis is at once apparent.

In a few cases the patient may have symptoms of sexual abnormalities, characteristic of adrenal tumors and in these cases we can make a diagnosis that it is highly probable the tumor is of adrenal origin in the known absence of primary adrenal tumors also existing.

The fact that these tumors are associated with

symptoms of sexual abnormalities makes it seem altogether possible they are of adrenal tissue origin. However, we cannot accept such a conclusion without some reservations. The kidney and adrenal being mesenchyme in origin and closely related it would seem possible for tumors of the kidney parenchyma by metaplasia to develop even functional characteristics of the adrenal cortex. This does not appear probable from our present knowledge of the behavior of tumors coming from tissue so highly specialized as that of the kidney. If, however, it remains a possibility we must not accept the functional behavior of renal tumors like that of adrenal tumors to be positive evidence of the neoplasms' adrenal tissue origin.

And here possibility of identification of such tumors with any great degree of certainty ends. There is left a relatively large group whose structure and cell type are indistinguishable from primary adrenal cortex tumors. At the same time they are identical in appearance with certain areas of hypernephromas whose origin may be traced to renal epithelium. They possess no clinical, gross or microscopic features by which we may determine thegroup to which they belong. In such

cases we must admit only the possibility of the growths arising from either misplaced adrenal glands in the kidney or adrenal rests. That they may have had their origin in renal epithelium is much more probable.

HYPERNEPHROMA OF RENAL ORIGIN

We have just discussed the hypernephromas of the kidney which we can say definitely arise from adrenal cortex tissue and those which possibly have their origin there. The latter, as pointed out, are equally likely to be of kidney epithelial origin.

There now remains to be discussed a group of tumors, generally placed under the heading hypernephroma, which we can trace directly to renal epithelium; and another group, closely related morphologically, having many characteristics of renal tubular epithelium but which have not been conclusively traced to renal tubules. The first group may be benign or malignant. The second are always malignant being characterized by a dendency to diffuse infiltration.

I have found in studying these tumors that it is not only possible to trace many of them to renal tubule

epithelium of the adult type but others may sometimes be demonstrated to originate in rests of foetal renal tubules occasionally found in the kidney.

It is also possible to find every gradation of development varying from simple adenoma to adenocarcinoma. Papillary formation is seen in the majority of these tumors. Those to be described as alveolar-adenocarcinoma lack this feature in typical cases. They differ, also in cell appearance from most hypernephroma.

Ewing has placed them in a separate group of renal neoplasms. However, their general morphology links them close with renal tubule epithelium. Moreover, in some of the typical papillary tumors with clear cells, transitions of structure and cell type result in an appearance sometimes having a striking resemblance to them.

For this reason it seems best to include them with the general group of hypernephroma, though certain evidence of their genesis cannot be produced.

It should be kept in mind that clinically the general hypernephroma group possesses all gradations of

evidence of malignancy. The majority of the typical ones, both of adenoma and carcinoma type, have a marked tendency to remain encapsulated. Extension is usually by way of the blood stream. The alveolar-adenocarcinomas tend to invade diffusely and belong in the more malignant class. However, the simple adenoma may potentially possess the same characteristics.

Hypernephromas from Foetal Renal Epithelial Rests.-

I have been unable to find in the literature any reports of the tracing of renal hypernephroma directly to foetal renal epithelium rests. However, a number of writers refer to the possibility of these rests being a source of kidney tumors belonging to this general group (Ewing, Karsner, Taggert).

If we assume the presence in the kidney of foetal renal epithelium bodies it would seem reasonable to believe that under certain conditions they might assume a neoplastic character. It is likely, however, that the tumor would soon over-run and obliterate evidence of the original tissue and only an unusual circumstance would allow us to trace the entire process in a single

specimen. This probably accounts for the lack of cases in the literature.

Occurrence of Fetal Tubules as Rests in Adult Kidneys.- The possibility of the presence of foetal rests of renal tubule epithelium in the kidney is easy to understand when we study the process of budding from the early collective kidney tubules which takes place to form tubules of a higher order and the repeated splitting of the nephrogenic bodies overlying these tubules (Keibel and Mall).

Kampmeier has described the normal failure of certain divisions of the metanephrogenic tissue in the kidney development to attach themselves permanently or at all to the tubular system and their usual atrophy later, which does not always occur. It is altogether possible such failure in the normal process of development is responsible for the presence of these foetal epithelial rests.

The finding of small areas in the kidney which appear identical microscopically with the tubules in foetal kidneys of four or five months is often described (Ewing, Karsner). They are pin head to pea

size, of a white or yellow color and sections show acini and tubules with small lumen. The cells are of typical embryonal character staining deeply, with relatively scant cytoplasm and large dark granular nuclei. Their shape is cuboidal or columnar. These rests are usually unencapsulated but are sharply demarcated from the surrounding adult renal epithelium.

Development of Tumors from Foetal Rests.- Occasionally hyperplasia is noted in these rests. The cells assume a more active appearance, become larger, more cytoplasm is present, and papillations may form. This begins a process which can be considered potentially neoplastic. Hertzler has described a similar process occurring in the thyroid with considerable frequency and in that location all stages of foetal epithelial rests may be followed to adenoma and at times to tumors having all the characteristics of glandular carcinoma.

In a specimen among the hypernephromata I examined at the Halstead Hospital tissue typical in appearance of foetal epithelium may be traced through the hyperplastid and papillary stage to areas developing into foam cells of the hypernephroma type.

This specimen was removed at operation from a man fifty-two years old. It was a thick-walled cyst 12 cm. in diameter having replaced the lower half of the kidney. A membrane from 2 to 7 cm. in thickness and of a yellow-gray color lined the cyst. A partition, partially dividing it into two locules, was covered with the same membrane. The cavity was filled with a hemorrhagic necrotic debris.

Examined microscopically the cyst lining was found to be of neoplastic tissue. The outer layer was made up of small acini and tubules of appearance identical to that seen in the kidney parenchyma of a four-month's foetus. Following this toward the center changes could be seen in the epithelium, the cells becoming larger and papillations developing. The core of these papillations was a single thin-walled capillary. On the inner surface the papillations gradually changed to longer papilli covered with large clear cells of the typical hypernephroma type. They were, however, hardly as large as those generally seen but even so, no smaller than the cells of many hypernephromata. That the tumor was at some time smaller and solid and that recurrent hemorrhage,

the result of degeneration, had distended and enlarged it is not unlikely but does not admit of proof.

Taggart, among a group of cases reported, mentions three solid tumors of this type occurring congenitally and he seemed to recognize the association of renal epithelium of a foetal character and hypernephroma-like tissue. He also pointed out a relation between such tumors and the congenital embryonal renal sarcoma of children containing heterogenous tissue.

The tumor just described was well encapsulated and no evidence of invasion of surrounding tissue was apparent. Whether or not it is essentially benign or potentially or actually malignant is hard to say. The patient is well two years after operation but this cannot be considered sufficient time to disprove the possibility of recurrence. It seems in all probability a cystadenoma of foetal epithelial origin. Its structure is such, however, as to show its close relation to other renal neoplasms with potential or actual malignant characteristics.

Hypernephroma from Focal Areas of Hyperplasia

Numerous writers trace all or the greater number of hypernephromas to adult renal tubule epithelium in some form. The small areas of focal hyperplasia found in sclerotic kidneys and sometimes considered as small adenomas have furnished the most accessible material through which this has been accomplished. Some writers (Stoerk, Manasse) claim to have traced them to normal renal tubules directly. Both Ewing and Karsner express doubt of the accuracy of this. Certain tumors of the alveolar-adenocarcinoma type reproduce the appearance of renal tubules to a marked degree. The latter stand somewhat apart from the generally accepted hypernephromas. Transitions between the two are seen, however, and it is altogether likely that they may originate from renal tubules through small adenomas or directly. The typical ones are made up of large, uniformly staining small granular cells.

Whether all of the typical hypernephromas coming from adult kidney tissue have theirorigin in focal areas of hyperplasia is not determined. The greater

number, however, appear in individuals of an age when small renal adenomas are more frequently present (Cutler).

Occurrence of focal areas of hyperplasia of renal tubules in sclerotic kidneys is well recognized. They have been found occasionally in large white kidneys. A few have been reported in kidneys of young adults apparently otherwise normal.

Frequency with which these are found has been variously estimated. It increases with the age of the patient. Ewing quotes Weichselbaum and Greenish as finding these structures in ten per cent of all individuals over 80 years old.

The cause of their development would seem in many cases to be due to an effort to compensate for damaged renal tubules. That this is not the only factor responsible is apparent from the fact that some are found in the kidneys of young individuals, the kidney showing no other change. A similar process is not uncommon in the liver and is nearly always associated with marked damage as is seen in cirrhosis.

Zehbe divides these foci of hyperplasia into two types, eg: those made up of papillations of large,

clear, fat-laden cells, and those of tubular and papillary structure with opaque, granular cells, resembling closely the normal tubular epithelium. Transitions between the two types are not unusual in the same tumor.

Sudeck is responsible for first tracing hypernephromas to these hyperplastic areas in the kidney. Many other writers have agreed with his conclusions (Stoerk, Zehbe).

Structure of these hyperplastic areas is usually of tubular type with an appearance closely simulating the convoluted tubules. The cell staining is more pronounced than the surrounding epithelium. The tubule or acini structures are separated by a capillary network and a few strands of fibrous tissue. The cells may not appear more than normally active and evidence of independent growth not apparent.

Development of an early stage of neoplastic growth is seen when papillations begin to extend into tubules and the cells increase in size and have dark granular nuclei. New tubules and acini are often formed

by budding from the primary tubules. Surrounding tubules are compressed by an increase in bulk of the hyperplastic area.

This represents the first stage of a process that can be regognized as neoplastic. From this tumors of varying appearance may develop. They are all closely related and the several types differ largely as to actual or potential malignancy the interpretation of this depending on the degree of advancing neoplastic characteristics.

Some continue to form structures made up of papillations and tubules covered with one or more layers of deep staining granular cells. They may be apparently benign papillary adenomas. If they show definite malignant tendencies they represent the granular cell carcinomas of Ewing. If the cell's character changes to a clear or foam cell type as will be described they may represent the clear cell adenoma, or even carcinoma, granting malignancy is evident. Some apparently are not malignant at the time of removal, failing to show invasive tendencies and failing to recur. These may be considered adenomas. It is often impossible, however, to definitely state

from examination, which are malignant and which benign. Recurrence sometimes follows removal of tumors seeming to be of typical adenomatous nature.

Development of structure of hypernephroma originating from focal areas of hyperplastic renal tubules can often be traced in a single tumor. It is necessary to understand this development in order to interpret a section made through a single plane of the tumor.

Hyperplasia, characterized by papillation and new tubule formation appears. At first the capillary stroma is covered by only one or two layers of cells which at first are granular and stain deep. If areas more advanced are examined it will be seen that new cell formation increases the thickness of the papilli and continues until they become many layers deep.

Here it is possible sometimes to trace the clear cell so characteristic of hypernephromas. In earlier tumors the cells are usually granular but as advancement takes place peripheral cells of foam cell type may appear. Other areas of the tumor may be made up entirely of foam cells. Study of numerous sections

often show every gradation from a tumor of papillary structure of deeply staining granular cells to the type usually seen made up totally of clear cells.

I have been able to trace this occurrence in a papillo-tubular adenoma removed from a woman 24 years old. Here the earlier development from renal epithelium could not be found in a definitely outline area of focal hyperplastic tissue. However, renal tubules having the appearance of those of the convoluted portion were found. Into some a single papillation extended. Adjoining this were areas in which the papillations were more extensive and branching present. This could be followed to the development of tangled masses of papilli which distended the tubules until their walls in most places could not be defined. The more advanced papillations were covered in some places with mixed clear and granular cells.

In other areas the structure was entirely of clear cells. Here they had increased in number until identification of papilli was difficult.

At the autopsy of a man 70 years of age one kidney was found associated with an orange size typical hypernephroma. The unaffected portion of the kidney

contained several tumors of the same type varying in size from 2 to 10 mm. in diameter. The opposite kidney was studded with about twenty small tumors, some appearing on the surface, others within the cortex or immediately beneath it. The smaller tumors had a loose papillary structure, the cells varying from pale, fine granular cells to clear cells of the foam cell type. The large tumor was made up of the same structure. Here, however, advancement of growth was more pronounced, the papillations in most areas covered with many layers of cells and closely packed. Sections through some areas resulted in an apparent arrangement of sheets and columns and perivascular formations.

Wright, by serial section, has demonstrated how hypernephromas cut at various planes may furnish this appearance. He was able to demonstrate a primary papillary structure in every case examined by him. This structure is clearly traceable to the papillary form yet has been frequently intepreted as an adrenal tumor structure.

Development of Foam Cells of Hypernephroma.- Foam cells are so often the only onew to be recognized in hypernephromas that the histological picture they

present has been accepted as characteristic. We can trace, in so many cases, their development from granular cells, however, that it is not possible to recognize them as the original cell. They have been repeatedly described as possessing a high lipoid and glycogen content. Nicholson has described this as due to degeneration caused by pressure occlusion of the thin-walled capillaries as a result of growth. It is true that in the loosely arranged stage sometimes described as papillary-cyst-adenoma the presence of foam cells is less common.

Though we are unable to say why the fat-laden clear cell appears it must not be considered the original type of cell. Many tumors still showing evidence of increasing in size are found in which the granular cells are not seen. It is difficult to say whether these have been overlooked and are present as the germinal cells responsible for growth or whether the foam cells are capable of division.

Alveolar Adenocarcinoma has been described by some writers as originating in adrenal rests. Others trace it to kidney tubules. As mentioned before, Ewing and Karsner do not believe there is conclusive proof of either assumption. The last case described furnishes

an excellent specimen for demonstrating the close relation of the clear-cut hypernephromas and this class of tumor.

In the larger of the numerous tumors in the kidneys areas were found having an alveolar structure. Instead of the clear or foam cells found in the papillary part of the tumor the cells forming the alveoli were large with pale staining, non-granular cytoplasm and round or oval deep staining nuclei. Transitions between these cells and the foam cells could be followed.

Lumina in the alveli were only occasionally present and are not well defined. While the general structure was alveolar, places could be found in which the growth was diffuse and infiltrating. In such cases diffuse invasion of the kidney may sometimes be apparent in the gross specimen.

This demonstrates a case of multiple papillary adenoma belonging to the hypernephroma type of tumors, but one of these has also progressed to a frank malignancy of the alveolar-adenocarcinoma type.

In other alveolar-adenocarcinoma which I have examined I have been unable to find evidence of the tissue from which they originated. It seems possible, at least, that some of these may come from small adenomas.

The possibility of direct transformation from renal tubules can not be denied.

Comparison of Hypernephromas of Foetal and Adult Tubule Origin.- Only one tumor among those examined gives evidence oforigin from foetal renal epithelium. If we compare the part of it which has developed into the typical appearance of hypernephroma with those tumors traced to adult renal tubules there is little found by which it might be differentiated, assuming it was not possible to trace it to its primary source. Ewing states it is possible that the foam cells of those tumors developing from foetal rests are smaller than the other variety. This is true in the case here described. It also happens that the cells of a hypernephroma are occasionally uniformly smaller than usual. Perhaps these develop from foetal rests but without more definite structures present revealing their parent tissue it is obviously impossible to differentiate these two classes with certainty.

A comparison of tumors of known adrenal and renal origin has been made under the heading of hypernephromas of adrenal origin. It must be remembered that tumors will occasionally be found in which no cellular or structural elements appear that indicates their origin and these we are unable to classify as

to genesis. Certain areas from all types are indistinguishable and careful search may be required to find areas possessing characteristic features marking their origin. The structural arrangement must be depended on largely for that.

SUMMARY

(1). There is a large group of kidney tumors of adults, generally referred to as hypernephromata, that are closely related morphologically but which vary in genesis.

(2). They more often originate from renal epithelium but in rare instances may arise in rests of adrenal tissue in the kidney.

(3). Those from renal epithelium may originate in embryonal rests or adult tissue.

(4). It is impossible to state definitely the origin of many hypernephroma. However, if abnormal sexual changes are evident their origin, while not certain, is, in all probability, in adrenal cortex tissue.

(5). If they possess a papillary or tubular structure they undoubtedly originate from renal epithelium.

(6). Those in which a papillary, tubular or acinar structure is not found may be traced in the vast majority of cases to tumors having such a structure and are thus of renal origin.

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